

F15028US-CNT

Rejection of Claims 12 and 13 under 35 USC 102(b)

The Examiner has rejected claims 12 and 13 under 35 USC 102(b) in view of Jinks (US Patent 4,810,488).

The Examiner states:

"Jinks teaches a crystalline material with a reduced particle size of 2 to 5 microns (Col. 6, Claims 6-10). The material is an anti-inflammatory steroid (Col. 6, Claims 6-10; Col. 1, lines 10-24). This teaching anticipated Claims 12 and 13."

Office Action mailed July 16, 2002, paper no. 6, page 2.

Applicants traverse this rejection.

To anticipate a claim, a single source must contain all of the elements of the claim (See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986)). Jinks discloses a product that is micronized in a Trost fluid energy mill (see Examples 1 and 2). Applicants disclose that ordinary fluid energy milling tends to convert crystalline material to its amorphous state (on page 2, lines 2 and 3). However, Applicants have discovered a method of producing highly crystalline material containing substantially no amorphous content. Applicants respectfully submit that Jinks does not contain all the elements of Applicants' claimed invention. In particular, Jinks does not disclose crystalline milled material containing substantially no amorphous content. *Not in claim 1*

Furthermore, Applicants submit that the Examiner is not appropriately applying the judicially accepted standard for novelty to their particular invention. The true test of any cited reference to show that an invention is anticipated is whether the reference places the invention, as claimed, in the possession of the public. The present claims are directed to crystalline material containing substantially no amorphous content and having a median particle size of less than 2 microns. By contrast, Jinks does not disclose crystalline milled material containing substantially no amorphous content. Nor does Jinks in any way suggest or predict how to successfully obtain crystalline milled material containing substantially no amorphous content. Applicants contend that the cited reference does not provide the requisite teaching needed to place their newly discovered crystalline milled material in possession of the public. *Claim 1, criticality*

In view of the above remarks, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 USC § 102(b).

FI5028US-CNT

Rejection of Claims 12 and 13 under 35 USC 103(a) over Jinks (US Patent 4,810,488)

The Examiner has rejected claims 12 and 13, under 35 USC 103(a) as being unpatentable over Jinks (US Patent 4,810,488).

The Examiner states:

"Jinks does not teach the exact particle sizes to have a median particle size of 1 or 2 microns. Jinks does teach the particle range to be below 10 microns and preferably 2 to 5 microns.

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to vary the particle size of the steroid to achieve a mean particle size of 1 or 2 microns. The active agent in [sic] micronized using a fluid energy mill (Col. 3, Examples 1 and 2).

One of ordinary skill in the art would have been motivated to do this [sic] prepare an active agent to be implemented in an aerosol formulation for inhalation into the human bronchial system.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made"

Office Action mailed July 16, 2002, paper no. 6, page 3.

Applicants traverse this rejection.

The courts have made it clear that in evaluating obviousness:

"Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure". In re Dow Chemical Co. v. American Cyanamid Co., 837 F.2d 471, at 473.

Applicants respectfully submit that Jinks discloses stable crystalline solvates of low alkanols (Col. 1, line 67 to Col. 2, line 2). However, there is nothing in Jinks to suggest using crystalline material containing substantially no amorphous content and having a median particle size of less than 2 microns. In fact, Jinks teaches away from crystalline material having a particle size of less than 2 microns as it is shown to be less stable and more susceptible to crystalline growth, than particles of about 5 and 10 microns. For example, commercial beclomethasone dipropionate with a particle size of less than 2 microns has a particle stability of 56.9%, whereas the compound with a particle size of less than 5 or 10 microns has a particle stability of 100% (see Col. 3, line 58). Also, Jinks does not in any way suggest or predict how to successfully obtain crystalline milled material containing substantially no amorphous content. Therefore, Jinks does not suggest crystalline milled material containing substantially no amorphous content and a median particle size of less than 2 microns.

F15028US-CNT

In view of the above remarks, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 USC § 103(a).

Rejection of Claim 14 under 35 USC 103(a) over Jinks (US 4,810,488) and Hagen (US 4767612)

The Examiner has rejected claim 14, under 35 USC 103(a) as being unpatentable over Jinks (US 4,810,488) in view of Hagen (US 4767612).

The Examiner states:

“...Jinks does not teach the active ingredient to be triamcinolone acetonide.

The Hagen reference teaches the micronisation of triamcinolone acetonide in a fluid energy mill. The particle size range of the micronized triamcinolone acetonide is 1 to 5 microns (Col. 2, lines 55-59). Triamcinolone acetonide is a steroid that is an anti-inflammatory and can be micronized for aerosol formulations (Col. 1, line 25-Col. 2, line 16).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare a crystalline particle of triamcinolone acetonide using a fluid energy mill.

One of ordinary skill in the art would have been motivated to do this to provide an aerosol formulation of an anti-inflammatory steroid that can achieve the same results as a similar steroid used for the same purpose.

Office Action mailed July 16, 2002, paper no. 6, pages 3 and 4.

Applicants traverse this rejection.

The courts have made it clear that in evaluating obviousness:

“Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant’s disclosure”. *In re Dow Chemical Co. v. American Cyanamid Co.*, 837 F.2d 471, at 473.

Applicants respectfully submit that neither Jinks nor Hagen suggest crystalline milled material containing substantially no amorphous content and having a median particle size of less than 2 microns. In fact, Jinks teaches away from crystalline material having a particle size of less than 2 microns as it is shown to be less stable and more susceptible to crystalline growth, than particles of about 5 and 10 microns. For example, commercial beclomethasone dipropionate with a particle size of less than 2 microns has a particle stability of 56.9%, whereas the compound with a particle size of less than 5 or 10 microns has a particle stability of 100% (see Col. 3, line 58). Also, highly crystalline material of the present invention has the advantage of not causing scale build up that is associated with amorphous material (see page 2, line 12-16).

F15028US-CNT

In view of the above remarks, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 USC § 103(a).

Rejection of Claims 1-16 under 35 USC 103(a) over Weishaupt (US 3897010) in view of Hagen et al. (US 4767612) and Capelle, Jr. et al. (US 6145765)

The Examiner has rejected claims 1-16 under 35 USC 103(a) over Weishaupt (US 3897010) in view of Hagen et al. (US 4767612) alone and further in view of Capelle, Jr. et al. (US 6145765).

The Examiner states:

"The Weishaupt reference teaches a method of milling material wherein a fluid energy mill is employed to micronized the material wherein the fluid is an inert gas at low temperature (Col. 2, lines 50-65; Col. 4, lines 19-34). The temperature of the fluid lies in a cryogenic range or a range of the liquefaction temperatures of the inert gas used in the method (Col. 4, lines 19-34). The purpose of the low temperature is to bring the milling material to a low temperature to embrittle the material to facilitate pulverization in the fluid energy mill (Col. 2, lines 66-Col. 3, line 17). The temperature of the fluid is reduced to a point such that the material to be milled is no longer plastically or elastically viscous but ruptures readily upon impact with a surface or another particle (Col. 2, line 66-Col. 3, line 17)..."

...The Hagen reference teaches the micronization of triamcinolone acetonide in a fluid energy mill. The particle size range of the micronized triamcinolone acetonide is from 1 to 5 microns (Col. 2, lines 55-59).

While the reference does not teach the complete temperature range, differences in temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such temperature is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955)....

...Further, the Capelle, Jr. reference teaches that the inert gas used as the fluid for a fluid energy mill can be helium (Col. 5, lines 20-31).

At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to incorporate helium as the fluid in the fluid energy mill. One of ordinary skill in the art would have been motivated to do this to choose a gas that is compatible with the material being processed and does not degrade the material upon contact with the fluid (Capelle, Jr., Col. 5, lines 20-31)."

Office Action mailed July 16, 2002, paper no. 6, pages 4 to 6.

Applicants traverse this rejection.

What the Examiner is applying here is nothing more than a restatement of the improper "obvious to experiment" standard of obviousness. *See In re Dow Chemical*, 837 F2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

F15028US-CNT

The courts have set forth that the motivating suggestion to combine elements so as to create the same invention must be explicit in the art. The court in Winner International Royalty Corp. v. Wang, No. 96-2107, 48 USPQ.2d 1139 (D.C.D.C. 1998) have stated:

"It is insufficient to prove that at the time of the claimed invention, the separate elements of the device were present in the known art. Rather, there must have been some explicit teaching or suggestion in the art to motivate one of even ordinary skill to combine such elements so as to create the same invention". Id 1140. (Emphasis added).

See also In re Laskowski, 871 F2d 115, 117, 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) where the court stated:

"the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification" (quoting In re Gordon, 733 F2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); and

In re O'Farrell 853 F2d 894, 7 USPQ 1673 (Fed. Cir. 1988) where the court made the observation that where the prior art gives no indication of which parameters are critical and no direction as to which of may possible choices is likely to be successful, the fact that the claimed composition falls within the scope of possible combinations taught therein does not render it unpatentably obvious.

Claims 1-11:

Prior to the present invention, problems had been encountered using conventional fluid energy milling to micronize crystalline material, in that the resulting micronized product contained a large amount of amorphous material (on page 1, lines 14-16 and page 2, lines 2 and 3). Micronized product containing a large amount of amorphous material caused scale build up in comparison to product containing substantially no amorphous material (see page 2, line 12-16).

Faced with this problem, Applicants have now discovered that carrying out fluid energy milling with helium at reduced temperatures affords highly crystalline product containing substantially no amorphous content. Applicants' solution enables the preparation of fine highly crystalline material.

Furthermore, the present application discloses (on page 5 lines 1 to 13) the unexpected advantage of using helium and reduced temperatures to produce highly

Optimization
not
obvious to
try

F15028US-CNT

crystalline product with substantially no amorphous content (see Run 4 and 5 in comparison to Runs 1 to 3).

Applicants respectfully submit that the cited art makes no suggestion of using fluid energy milling to produce highly crystalline material i.e. material containing substantially no amorphous material. For example, Weishaupt et al. is directed to the jet milling of synthetic resins at low temperatures. A person of ordinary skill in the art upon reading Weishaupt, Hagen et al, and Capelle, Jr. et al. would not have been led to use a milling fluid comprising helium at reduced temperature, because there was no desire to produce a fine, highly crystalline material product. The Examiner's rejection is therefore apparently based on hindsight, having regard for to the Examiner's knowledge of the present invention. It is well established under decided U.S. case law, than an obviousness rejection based on hindsight is improper.

improper/
hindsight

Since there is no suggestion in the art to produce a fine, highly crystalline material product by fluid energy milling, there clearly would have been no motivation for a person of ordinary skill to modify the teaching of Weishaupt, Hagen et al, or Capelle, Jr. et al. to obtain Applicants' invention. Absent such motivation, it is clear that a *prima facie* case of obviousness is not generated by the cited art.

Claims 12-16:

Applicants respectfully submit that neither Weishaupt, Hagen et al, or Capelle, Jr. et al. suggest crystalline milled material containing substantially no amorphous content and having a median particle size of less than 2 microns. For example, Weishaupt et al. discloses synthetic resins. In fact, the art (e.g. Jinks) teaches away from crystalline material having a particle size of less than 2 microns as it is shown to be less stable and more susceptible to crystalline growth, than particles of about 5 and 10 microns. For example, commercial beclomethasone dipropionate with a particle size of less than 2 microns has a particle stability of 56.9%, whereas the compound with a particle size of less than 5 or 10 microns has a particle stability of 100% (see Col. 3, line 58). Also, highly crystalline material of the present invention has the advantage of not causing scale build up that is associated with amorphous material (see page 2, line 12-16).

mean particle size 2^e
one particular drug

In view of the above remarks, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 USC § 103(a).

F15028US-CNT

In view of the foregoing remarks, Applicants submit that this application is in condition for allowance. A favorable action passing this case to issue is therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicants' agent invites the Examiner to contact him at the number provided below.

CHANGE OF ATTORNEY/AGENT

Applicants also request that future communications regarding this application be directed to the following:

Peter L. Dolan, Ph.D. J.D.
Aventis Pharmaceuticals Inc.
Patent Department
Route 202/206N,
P.O. Box 6800
Bridgewater, NJ 08807
908-231-2470 (Tel.)
908-231-2626 (Fax)

Respectfully submitted,



Date: Oct 15 2002

Peter L. Dolan, Ph.D. J.D.
Registration No. 46,307

Marked Up Version of Re-Written Claims

1. (Amended) A method for producing a fine, highly crystalline material product, the method comprising fluid energy milling a crystalline material using a milling fluid comprising helium ~~at reduced temperature, wherein the temperature of the milling fluid is between -30°C and -120°C.~~